ferment in Darwin's time: Where did we come from and where are we going?

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Where Are the Limits of Life?

Extremophiles: Microbial Life in Extreme Environments
Edited by Koki Horikoshi and William D. Grant
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Research during the last thirty years has demonstrated that life's boundaries reach far beyond the conditions comfortable for human existence. In particular, prokaryotic microorganisms are highly adaptable to diverse environmental conditions. Halophilic microorganisms have been isolated from environments with salt concentrations ten times higher than seawater, hyperthermophilic bacteria and archaea thrive at temperatures above 85°C, and a pH of 1 is comfortable to some acidophiles. These conditions create unique scientific obstacles to the collection, isolation, and cultivation of organisms from such environments. Furthermore, since greater than 90% of prokaryotes remain as-yet uncultivated, it is a major challenge to the scientific community to determine the characteristics that allow some organisms to thrive in these environments while others vanish.

The recently published book *Extremophiles: Microbial Life in Extreme Environments* describes some of the prokaryotes that have carved out niches in highly selective environments. The aim of the editors is to provide a comprehensive overview of the current knowledge of various groups of cultivated "extremophiles," including the ecology, physiology, and potential applications, especially of enzymes derived from the microbes that are living under these conditions. Because there is not a unifying organizational format for each chapter, this objective is met to varying degrees of success in the different chapters. For example, there is a very good overview presented for the psychrophiles, including their distribution and isolation, physiology, and molecular biology. Conversely, possibly because of the very diverse nature of the responsible prokaryotes, the same information and organization is lacking in the chapter on the reduction of metal cations and oxyanions by anaerobic and metal-resistant microorganisms. The substantial overlap of information in several of the chapters, as well as the choice of chapters, demonstrate what has become clear in recent years, that the term "extremophiles" is a bit of a misnomer.

"Extremophile" conjures up visions of harsh environments where our own existence would be questionable at best. This is certainly true for the genera of prokaryotes covered in a bulk of the text. However, the inclusion of chapters such as the one on solvent tolerance in *Escherichia coli* suggests that organisms from virtually all prokaryotic branches on the tree of life are capable of survival and/or growth under so-called extreme conditions, thereby rendering the term useless. Extreme conditions may be transient or permanent and will greatly influence the acquired adaptations. One could make the argument that life under "competitive conditions" and "extreme conditions" is essentially the same since the point at which one organism is no longer able to compete creates an extreme condition—at least for that particular organism. Extremophile means "lover of extreme conditions." Because the definition of extreme conditions will vary from organism to organism, it may be more useful to ask the question, Where are the limits of life?

There are a number of books that address this question, notably *The Outer Reaches of Life* by John Postgate (Cambridge University Press, Cambridge, 1994) and the recently published *Life on the Edge* by Michael Gross (Plenum Trade, New York, 1997). Both books do an excellent job of covering the broad topic of life's adaptations to diverse environments. Though geared toward readers with a less technical background than the target audience of *Extremophiles*, both books adeptly explain in a clear language the salient features of survival strategies used by prokaryotes adapted to very specific stress conditions. *Extremophiles* provides the reader with an in-depth overview of cultured organisms from particular niches, specific isolation and culturing methods, or detailed listings of identified biotechnologically interesting enzymes from cultivated organisms.

The proliferation of research articles, publication of books, and a new peer-reviewed journal, *Extremophiles*, demonstrate the increasing interest in the study of microorganisms from diverse habitats. While Horikoshi and Grant limit their discussion to cultured prokaryotes, 16S rDNA analysis of various environmental niches has revealed that less than 10% of all microorganisms have been isolated and cultured in the laboratory. It is very interesting to note that, despite the 16S rDNA signatures from uncultivated organisms added to the now phylogenetic "bush" of life, there are no significant divergences creating new branches (Pace, Science *276*, 734–740, 1997). Does this suggest scientists have been successful in cultivating representatives from all the branches? Organisms comprising a hypothetical new branch are likely to have adapted novel metabolisms to meet unique challenges and are likely to occur in less explored environments. The editors of *Extremophiles* missed an excellent opportunity to touch upon this exciting area of research. 16S rDNA techniques have not only allowed scientists to identify uncultivated organisms, but they have also provided tools allowing them to determine the presence of specific organisms in a given environment. These analyses are an important development in determining microbial community structure and possible roles individual members may play in the environment.

The most recent development promising vast amounts of new information about cultivated, as well as uncultivated, microorganisms is the sequencing of whole genomes. To date, 18 prokaryotic genomes have been sequenced; four are of hyperthermophiles. Two hundred sequenced genomes are expected by the year 2000. For a majority of the sequenced genomes, less than

50% of the open reading frames (ORFs) have been linked to a known function. Even within the genome of *E. coli*, the most extensively studied bacterium, less than two-thirds of the annotated protein-coding genes showed significant similarity to genes with ascribed functions. These data, suggesting an overwhelming amount of information in the form of ORFs, could be useful for biotechnological, pharmaceutical, and research sciences and may also provide clues to the early evolution of life on earth.

Extremophiles would have been strengthened by a broad overview of the field beyond the cultured organisms, including information of not-yet-cultured organisms and potential uses of genome comparisons to identify features that are shared by the various "extremophiles." However, the in-depth descriptions of growth conditions and isolation techniques will aid microbial ecologists in the isolation of as-yet-uncultured organisms with DNA sequence homologies to cultured organisms discussed in the text. While gene sequence information was not discussed in the text of *Extremophiles*, those who would benefit most from the book are scientists using gene-based probes to study microbial ecology, genome sequencing teams who use known sequences for the annotation of genomes, and biotechnology companies using sequence information for the discovery of single- and multiple-gene products. In addition, researchers involved in the study of microbial adaptations may find the text useful. In summary, what the text highlights very well, if in an indirect sense, is that we have much to learn about the organisms that inhabit these "harsh" environments. Who are the members of the community, how do they interact, and how do they impact their environments? These are questions that are begging to be addressed in the next text on "extremophiles."

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Stem Cell Manifesto

Stem Cells
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On the rare occasions when scientists get together to talk about stem cells, it is almost guaranteed that at some point a heated argument will break out. It will be couched in appropriate scientific language, but the cut and thrust of the debate is instantly recognizable to any three-year-old: "I've got a stem cell," "No you haven't," "Yes I have," "No you haven't," and so on for as long as the session chairman allows. The protagonists become ever more flushed and resentful, and the audience look on with either bemusement or amusement, depending on whether it is the first time they have witnessed such a scene or whether they are regular spectators. This sort of thing gives the field a bad name, which is a shame since it is not only of great intellectual interest, but also of considerable practical importance. It also explains why meetings on stem cells are not held very often.

As a way of bringing, if not lasting peace, at least a temporary cessation of hostilities, I propose a stem cell manifesto of "more experiments, less philosophy." Essentially all the important concepts about stem cells were published in the 1960s and early 1970s, and this early work is still worth reading and relevant today—names like Leblond, Lajtha, Till, and McCulloch come to mind immediately. Yet some people are still so busy worrying about how to define a stem cell that they fail to grasp the important advances that are taking place at an ever faster pace around them. Chris Potten deserves the accolade of "the world's greatest living stem cell philosopher" and his recent book *Stem Cells* should be the final word of the philosophical era. The experimental era is already well underway.

So what are the cells that are causing all the trouble? In adult tissues they are cells that have essentially unlimited self-renewal capacity and also the ability to produce more differentiated daughter cells. Classically stem cells have been studied in the hemopoietic system, epidermis, testis, and gut, tissues in which there is constant and rapid turnover of the cell population and in which the most differentiated cells are unable to divide at all. Now, however, there is more appreciation that stem cells are also present in tissues that were previously thought to be incapable of regeneration, such as the nervous system, and in those that only undergo significant cell turnover in response to injury, such as the liver. Developmental biologists think about stem cells a little differently, the primary characteristic of stem cells in the embryo being to found specific lineages, rather than to self-renew; paradoxically, it is as a result of differentiation that embryonic stem cells give rise to the stem cells of adult tissues.

Why are stem cells interesting? To understand differentiation in many postembryonic tissues, we need to know what controls stem cell fate, and the specific questions to be answered are of interest to biologists in a wide range of disciplines, from genetics, through cell and developmental biology to pathology. In the steady state, stem cell divisions generate an equal number of stem and differentiating daughter cells and thus stem cells have the property of asymmetric division, whether on a population basis or as an invariant feature of every mitosis. We need to understand the extent to which stem cell fate is determined autonomously or is subject to environmental regulation; how specific differentiation pathways are selected; whether a given differentiation state is plastic or invariant; and the relationship between the cell cycle and differentiation. Stem cells are also of tremendous practical importance for tissue repair and replacement, and for gene therapy: to achieve sustained production of therapeutic genes in self-renewing tissues, it is essential that stem cells are included in the target population.